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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/945,517	08/30/2001	Tiansheng Li	A-803	2680

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U.S. Patent Operations/ CAC
Dept. 4300, M/S 27-4-A
AMGEN INC.
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EXAMINER	
SCHNIZER, HOLLY G	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 10/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/945,517	LI ET AL.	
	Examin r	Art Unit	
	Holly Schnizer	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 August 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3 & 4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

Claims 1-27 are pending and have been considered on the merits in this Office Action.

Information Disclosure Statement

The information disclosure statement filed April 16, 2002 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. In the present case, reference C10 of the IDS has not been considered because a copy of the publication is not present in the file and the relevant pages of the publication are not provided in the Form PTO-1449. The examiner was able to obtain and consider all of the other references cited in the IDS as indicated by the initialed PTO form 1449. Reference C10 has been crossed out to indicate that it was not considered. The initialed copy of the information disclosure statements filed April 16, 2002 and February 20, 2003 are attached to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of "improved stability" in Claims 1 and 13 is not clear because a reference point from which "improved stability" is measured is not provided. This rejection could be overcome by adding a phrase such as, "as compared to a formulation that does not contain methionine" after "improved stability". Claims 2-12 and 14-27 are also rejected since they depend from these rejected claims yet do not correct the deficiencies.

Claim 4 recites the limitation "said active *ingredient*" (emphasis added) in line 2. There is insufficient antecedent basis for this limitation in the claim. Claims 5-8 are also rejected since they depend from the rejected claim yet do not correct its deficiencies.

The metes and bounds of Claim 27 is unclear. The Specification indicates that a biologically active agent is considered to be proteins, lipids, small molecules, carbohydrates, nucleic acids, and analogs thereof. The claim is drawn to a method of stabilizing a composition of biologically active agent. Therefore, the claim appears to encompass a method of stabilizing a composition containing a protein, lipid, small molecule, carbohydrate, nucleic acid, or analog thereof. However, line 3-6 of Claim 27 state that methionine is added to the composition in amounts sufficient to inhibit oxidation of methionine residues in the amino acid sequence of said biologically active agent. Since lipids, some small molecules, carbohydrates, nucleic acids, and their

analogs do not contain amino acid sequences, the claim is unclear as to the scope of what biologically active agents the method is used to stabilize. Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 13-15 and 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. .

As stated above, in order to meet the requirements of 35 U.S.C. 112, the Specification must contain *a written description of the invention and the manner and process of making and using it, in such full, clear, concise, and exact terms* as to enable any person of skill in the art to use the invention. In the present case, the Specification fails to provide a written description of the claimed pharmaceutical formulations comprising carbohydrates, lipids, nucleic acids, or small molecules (other than peptides and proteins) in full, clear, concise, and exact terms because the Specification does not teach what kinds of small molecules (other than specific proteins), carbohydrates, lipids, or nucleic acids can be used or how they can be used. Carbohydrates, lipids, nucleic acids, and "small molecules" encompass a wide range of products having diverse functions and uses, and the present Specification does not provide any teaching or

examples of what products were contemplated. Thus, the Specification fails to meet the requirements of written description.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Skrabanja et al. (U.S. Patent No. 5,929,028, 7-27-99; ref. A19 of the IDS filed February 20, 2003.

Skrabanja et al. discloses a pharmaceutical formulation comprising a bioactive agent (luteinizing hormone, thyroid stimulating hormone, follicle stimulating hormone, chorionic gonadotropin) and methionine to stabilize the protein (see abstract). Skrabanja et al. do not indicate that human serum albumin was added to the formulations described therein. The methionine concentrations disclosed in Skrabanja et al. are 1-10 mM (Col. 4, line 67). Skrabanja et al. states that the methionine is added

to the protein formulation in order to stabilize the protein (see abstract and claims 1 and 2).

Claims 1-4, and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Takruri (U.S. Patent No. 5,272,135, Dec. 21, 1993; ref. A8 of the IDS filed April 16, 2002).

Takruri discloses a method of inhibiting oxidation of a protein (bioactive agent) in a pharmaceutical preparation wherein methionine is added in a sufficient amount to inhibit the oxidation of methionine residues in the protein (see abstract). Takruri provides a specific example of adding methionine at concentrations within the range of present claim 2 to pharmaceutical formulations containing epidermal growth factor (see Example III). Present Claims 13-16 are drawn to formulations with the intended use of multi-dosages.

Claims 1-4, 13-16, and 27 are rejected under 35 U.S.C. 102(e) as being anticipated by Chen et al. (U.S. Patent No. 6,525,102, filing date, May 2001).

Chen et al. teach a pharmaceutical formulation containing interleukin-2 (a bioactive agent) and 5 mM methionine wherein the formulation has improved stability and does not contain human serum albumin (see Col 30, lines 54-67). Many of the formulations disclosed in Chen et al. also contain preservatives such as 0.9% (w/v) benzyl alcohol (the formulations in Table 6 have IL-2, 5 mM methionine, and various preservatives, for example). The formulations disclosed in Chen et al. appear to have

the same components as the formulations claimed in present Claims 13-15 and are therefore patentably indistinguishable from the claimed formulations having the intended use of multiple dosages.

Claims 1-8, 13-21, and 27 are under 35 U.S.C. 102(e) as being anticipated by Papadimitriou (U.S. Publication No. 2002/0037841; published March 28, 2002; filed May 11, 2001; ref. A20 of IDS filed February 20, 2003).

Papadimitriou et al. discloses a pharmaceutical formulation comprising an erythropoietin (EPO) product having a sequence identical to presently claimed SEQ ID NO:1 (see SEQ ID NO:1 of Papadimitriou) and 1-20 mM methionine (p. 4, [0048]) at pH 5.5-7.0 (p. 1,line 9 of [0009]; p. 21, claim 57). Papadimitriou discloses a specific formulation comprising EPO and 1 mM methionine at pH 6.2 (p. 17, Table 4 and [0211]. Papadimitriou states that methionine acts as an anti-oxidant and stabilizes EPO (p. 17, [0211]). Papadimitriou teaches that the formulation disclosed therein can contain a non-ionic detergent such as polysorbate 20 or polysorbate 80 up to 0.1% (w/v) (p. 4, [0049] and p. 3, Col. 1) and claim 57 therein is drawn to a formulation containing EPO, 10 mM methionine and 0.01% pluronic F68. Papadimitriou teaches the formulations may be made as multi-dose formulations (p. 2, [0012]) and that preservatives are added to the pharmaceutical formulations disclosed therein to prevent bacterial growth (p. 2, [0021]). It is noted that some of the examples of formulations provided in Papadimitriou do not contain benzyl alcohol and therefore are considered to contain 0% benzyl alcohol (see present claim 19). Human serum albumin is not a component of any of the

formulations taught in Papadimitriou and Papadimitriou teaches that human serum albumin increases the risk of viral infections and allergic reactions in formulations that contain the additive (p. 1, [0006]).

Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Van den Oetelaar et al. (EP 0 431 663, 6-12-91).

Van den Oetelaar et al. teach a pharmaceutical formulation comprising 3 mM methionine (0.5 mg/ml; Ex. 1) and any one of the antidepressants mirtazapine, mianserin, septiline, or amitriptyline (see abstract). The antidepressant compounds are considered small molecules. Van den Oetelaar et al. teaches that the methionine stabilizes the small molecules from light, high temperatures, time and peroxides (it acts as an anti-oxidant) (see abstract).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (U.S. Patent No. 6,525,102, filing date, May 2001) and/or Papadimitrou ((U.S. Publication No. 2002/0037841; published March 28, 2002; filed May 11, 2001; ref. A20 in IDS filed Feb. 20, 2003) in view of Kinstler et al. (U.S. 6,586,398, filing date 4-7-2000).

The teachings of Chen et al. and Papadimitrou are discussed above. Chen et al. and Papadimitrou provide evidence that it was well known in the art at the time of the invention that methionine could be added to protein formulations in general (see Chen et al.) and EPO formulations specifically (see Papadimitrou) to decrease oxidation and increase protein stability. Papadimitrou teaches that any EPO with the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells can be used in the formulations disclosed therein (p. 2, [0023]).

Chen et al. and Papadimitrou do not teach a formulation containing methionine and the novel erythropoiesis stimulating protein (NESP) with the sequence of SEQ ID NO:2 specifically.

Kinstler et al. teach the sequence of NESP that is identical to SEQ ID NO:2 of the present invention and states that although the half-life of NESP offers the advantage of less frequent dosing relative to EPO, there are still potential indications which may

require an even longer therapeutic half-life than NESP currently demonstrates (Col. 1, lines 37-41).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to make and use a formulation as disclosed in Chen et al. and/or Papadimitrou wherein the protein was NESP having the sequence of SEQ ID NO:2 as disclosed in Kinstler et al. Kinstler et al. provide evidence that it was known at the time of the invention that NESP had had an improved half-life over EPO but that there were still treatments that required an even longer half-life than NESP currently offered. Chen et al. and Papadimitrou provide a well-known solution to increasing the half-life of a related protein (EPO) and other proteins. Thus, one would have been motivated to combine the Chen et al., Papadimitrou, and Kinstler et al. references in order to further improve the half-life of NESP for treatments that require longer half-lives such as taught in Kinstler et al.

Claims 1-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shoemaker (U.S. Patent No. 4,835,260; ref. A18 of IDS filed Feb. 20, 2003) in view of Takruri et al. (U.S. 5,272,135; ref. A8 of IDS filed April 16, 2002) or Kinstler et al. (U.S. 6,586,398, filing date 4-7-2000).

The teachings of Takruri et al. have been described above. Takruri et al. teaches a method of inhibiting oxidation of proteins that contain a methionine residue by adding methionine in a sufficient amount to inhibit the oxidation of the methionine residue in the protein thereby increasing the protein's stability (see Col. 3, lines 25-35).

Takruri et al. do not teach formulations comprising erythropoietin (EPO) or novel erythropoiesis stimulating protein (NESP).

Shoemaker describes EPO proteins wherein a methionine residue has been substituted with another amino acid to stabilize the protein.

Kinstler et al. teach the sequence of NESP that is identical to SEQ ID NO:2 of the present invention and states that although the half-life of NESP offers the advantage of less frequent dosing relative to EPO, there are still potential indications which may require an even longer therapeutic half-life than NESP currently demonstrates (Col. 1, lines 37-41).

It would have been obvious to one of ordinary skill in the art at the time of the invention to add methionine to EPO and NESP formulations in order to stabilize the proteins. The EPO and NESP sequences were well known at the time of the invention as evidenced in Shoemaker and Kinstler et al. One of ordinary skill in the art would have recognized the broad teachings of Takruri et al. as being applicable to any protein having a methionine. Shoemaker provides evidence that those of ordinary skill in the art were targeting a methionine residue in EPO as a potential point for enhancement of protein stability. One of ordinary skill in the art would have been motivated to improve the stability of EPO formulations by adding methionine as taught in Takruri et al. rather than making the mutations as taught in Shoemaker because Shoemaker teaches that methionine is a highly conserved part of the sequence and that the EPO is highly sensitive to amino acid changes (see Col. 2, lines 1-25). One of ordinary skill would have had a reasonable expectation of success given the successful results of Takruri et

al. and the suggestion in Takruri et al. that the method could be applied to proteins in general.

Conclusion

No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Tuesday, Thursday, and Friday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

Holly Schnizer
October 14, 2003

CHRISTOPHER S. F. LOW
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